having been cancelled *without prejudice* pursuant to the Examiner's restriction requirement and Applicant's decision to elect with traverse to prosecute the invention of claims 1-9. Upon the indication of allowable subject matter, and before the issuance of any patent from this application, Applicant will give consideration to filing a divisional application for the claimed subject matter cancelled in this paper. The specification has been amended to reflect Applicant's claim of priority from the original PCT application PCT/US98/18284, as well as provisional application serial number 60/057,921. No new matter has been added by the present amendment.

The Examiner has acknowledged Applicant's election to prosecute claims 1-9 in this application and has otherwise made the restriction requirement final. In response, Applicant has cancelled claims 10-24 in order to expedite prosecute of the instant application to allowance.

Separately, the Examiner has rejected claims 1-9 under 35 U.S.C. §103 as being obvious over Epstein, et al., U.S. No. 3,715,361 ("Epstein") and GB 841,697 ("GB '697"), in view of Bagal, et al., ("Bagal") and Hussain, U.S. No. 4,464,378 ("Hussain"). The Examiner relies on Epstein for putatively disclosing that ibogaine and its derivatives are analgesic agents and consequently, the agents are therefore useful in treating or alleviating pain. The Examiner relies on GB '697 for teaching that ibogaine is an analgesic agent and therefore is useful in an analgesic composition for treating or alleviating pain. The Examiner acknowledges that the prior art does not expressly disclose the employment of noribogaine alone or in combination with an opioid antagonist in a method of treating a patient to alleviate pain. The Examiner cites Bagal for disclosing that noribogaine is a known active metabolite of ibogaine and that noribogaine enhanced morphine antinociception was more pronounced than with comparable ibogaine treatment. Finally, the Examiner cites Hussain for teacing that opioid antagonists such as naloxone, naltrexone and nalorphine are well known analgesics and therefore useful in a method of treating or alleviating pain in a patient.

Given the teachings of the prior art, the Examiner contends that one of ordinary skill would have been motivated to employ noribogaine alone or in combination with an opioid antagonist such as naloxone, naltrexone or nalorphine in a method of treating a patient to alleviate pain and to optimize the effective amounts of agents in the composition herein to be

administered. Applicant respectfully traverses the Examiner's rejection.

The present invention relates to the unexpected discovery that noribogaine, in contrast to ibogaine, may be used as a non-addictive analgesic agent, alone or in combination with an opioid antagonist. Without being limited by way of theory, it is believed that noribogaine functions, at least in part, as a full *mu* opiod receptor *agonist* without addictive properties. This stands in contrast to ibogaine, which exhibits weak activity as a *mu* opoid receptor agonist and has a different pharmacological profile than does noribogaine. Consequently, the present invention makes use of noribogaine's unique activity and represents a particular effective method for alleviating pain, an advance in the art and an exciting improvement over the treatments of the prior art. Methods which make use of noribogaine in combination with an opioid antagonist represent alternative embodiments of the present invention.

In contrast to the Examiner's arguments, the present invention is clearly patentable and non-obvious over the teachings relied upon by the Examiner. The Examiner cites Epstein and GB '697, in view of Bagal and Hussain as rendering the present invention obvious. It is respectfully submitted by Applicant that Epstein and GB '697 do not teach or suggest the present invention, that Hussain, by failing to even mention the present invention, does not obviate the deficiencies of Epstein and GB '697, and if one goes further and asserts Bagal against the present invention, the combination of references actually *teaches away* from the present invention. A detailed discussion of the patentability of the present invention follows.

It is clear from the art and even the Examiner's office action that none of the references teach noribogaine as an analgesic, alone or in combination with an opioid antagonist as claimed. A review of Epstein shows that this reference does not even disclose noribogaine. Note that Epstein discloses a series of acyl derivatives of 10-methoxyibogamine analogs for use as potential analgesic analogs. Epstein clearly does not disclose noribogaine, which is presented in the present specification on page 6. In the chemical compounds which are disclosed by Epstein at at columns 1 or 2 or otherwise described in Epstein, noribogaine is not discussed or suggested. Moreover, in each analog which is disclosed by Epstein, the O-methyl group on the benzene ring of the molecule is always an O-methyl group. Epstein completely failed to appreciate the potential activity of noribogaine or that the O-methyl is advantageously converted to a hydroxyl group to provide the activity of noribogaine. Because Epstein does

not disclose noribogaine or the chemical conversion of the O-methyl group which may be advantageously employed in noribogaine to provide its activity, Epstein clearly does not disclose or suggest the present invention.

GB '697 describes the use of a number of narcotic morphine analogs (including morphine) in combination with ibogaine or tabernanthine for analgesic use. GB '697 does not disclose noribogaine as an analgesic agent alone, and further suggests the use of an addictive analgesic agents having morphine-like characteristics in combination with ibogaine or tabernanthine. This disclosure is actually duplicative in some measure of Bagal, discussed infra. In preferred embodiments of GB '697, as set forth in examples 1-2 5, 7-8 and 11, the use of morphine is described in combination with ibogaine or tabernanthine. This teaching is in complete contrast to the present invention inasmuch as the present invention relies on noribogaine as a *nonaddictive* analgesic alone in the first instance, and when combined with another agent, that agent is an opioid antagonist- an *opioid inhibitor*- not an *agonist* such as morphine. Thus, GB '697 clearly does not teach the present invention for it fails to teach or suggest noribogaine even obliquely, and when it discloses ibogaine, ibogaine is disclosed in combination with another agent, that agent being the addictive analgesic agent morphine. GB '697 clearly does not obviate the deficiencies of Epstein in failing to disclose or suggest the present invention.

Turning to Hussain, this reference completely fails to even disclose or suggest noribogaine and consequently, fails to disclose or suggest the present invention. In the present invention, the use of noribogaine *alone or in combination* with an opioid antagonist is claimed. The use of an opioid antagonist *only* in combination with noribogaine is claimed. None of Epstein, GB '697 or Hussain teaches that noribogaine may be used as an analgesic, alone or in combination with an opioid antagonist. Consequently, none of these references teaches or suggests the present invention and the present invention is non-obvious over the disclosure of these references.

Turning to Bagal, it is respectfully submitted that this reference does not disclose or suggest the present invention. In the first instance, Bagal is prior art under 102(a), inasmuch as the Bagal paper published on November 25, 1996, a date which is less than a year after the

provisional application from which the present application claims priority was filed.[1] Moreover, a review of the Bagal disclosure evidences that the teachings of this reference actually *teach away* from the present invention. Bagal discloses the impact of ibogaine and noribogaine on other opiate actions. Bagal investigated the potentiation of ibogaine's effect on morphine analgesia. In particular, Bagal describes experiments which investigated the effects of ibogaine and noribogaine on morphine-induced antinociception. The experiments of Bagel clearly resulted in the finding that the co-administration of ibogaine and morphine resulted in an enhancement of morphine action which was dose dependent (see page 259 right column and 260, left column). Experiments involving noribogaine, which are described on pages 260-261, evidence that noribogaine exhibited *only slight antinociceptive properties alone* and minimal effects on *morphine* antinociception when given 19 hours earlier (Bagal, page 261, top right column), but significant antinociceptive activity when co-administered with morphine.

Bagal concluded that noribogaine, when co-administered with morphine, simulated the results obtained with ibogaine-morphine co-administration. Thus, Bagal concluded that both ibogaine and noribogaine increased morphine antinicieption when co-administered with morphine. Bagal also concluded that a 19 hour pretreatment with noribogaine showed only a slight ("if any") enhancement of morphine antinociception (p. 261, right column, bottom). Bagal concluded that noribogaine itself did not possess significant antinociceptive activity, but ND significant antinociceptive effect only when combined with morphine. One of ordinary skill, reviewing Bagel, would conclude that the administration of noribogaine may be used in combination with morphine to provide significant antinociception activity, but that noribogaine *itself* was not a viable analgesic. This teaching completely contradicts the present invention.

Thus, Bagal does nothing to obviate the deficiencies of Epstein, GB '697 or Hussain. Indeed, if one of ordinary skill could draw any conclusions from Bagal, it is that noribogaine alone should not even work in the present invention, and that if noribogaine was to be used in an analgesic application, it would be in combination with morphine. Yet, Applicant has discovered that not only does noribogaine work alone (a concept which is clearly contravened

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[1] Although it is Applicant's view that Bagal does not impact the present invention or otherwise render the present invention invalid, either alone or in combination, Applicant reserves the right to make the appropriate showing to remove Bagal as a reference against the present application.

by the conclusions reached by Bagal), but that noribogaine is also effective as an analgesic in combination with an opioid *antagonist*, also a concept which is contravened by the putative requirement of Bagal that an opioid *agonist* such as morphine is required. Based upon the teachings of Bagal and the conclusions of the routineer taken from that reference, Applicant respectfully submits that Bagal actually *teaches away* from the present invention, in the first instance by suggesting that noribogaine cannot be used *alone* as an analgesic and in the second instance by suggesting that noribogaine can be effective when combined with an opioid *agonist* such as morphine, not a morphine *antagonist* as is suggested by the present invention.

A combination of the teachings of the references cited against the instant application does not render the present invention obvious. Either the references are devoid of any teaching of noribogaine, or where noribogaine is disclosed, those references actually teach that the present invention is not a viable approach. Consequently, because the art is wholly deficient and completely fails to teach or suggest the present invention, Applicant respectfully submits that the present invention is patentable.

For the above reasons, Applicants respectfully assert that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

Applicants have cancelled 15 claims in the present application. No fee is therefore due for the presentation of this amendment. A petition for a three month extension of time is enclosed as is the appropriate fee. If any fee is due or any overpayment has been made, please charge/credit Deposit Account No. 04-0838.

Respectfully submitted,
Coleman Sudol Sapone, P.C.

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: "Commissioner for Patents, Washington, D.C. 20231" on January 15, 2003.

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Henry D. Coleman

Appendix

Please cancel claims 10-24 of the present application and amend the specification as follows:

In the Specification:

After the title, please insert the following paragraph as the first paragraph of the present application:

--Related Applications

The present application is a §371 of PCT/US98/18284, filed 3 September 1998, which claims priority from provisional application serial number 60/057,921, filed 4 September 1997.--